

REMARKS

Reconsideration and allowance of the present application is respectfully requested in view of the foregoing amendments and the following additional remarks which have addressed all the issues raised in the May 24, 2006, Office Action or otherwise have rendered them moot.

Claim 6 is canceled. Claim 1 is amended and claims 34-38 have been newly added. Claims 1-4, 9, 34 – 38 are now under consideration in this application.

Claims 1-3, 7, and 9 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ferreira et al., (FASEB J, 1998, 12:231-242) as evidenced by Gajhede et al. (Ref. AD1 of 6/20/2002 IDS).

Claims 1-4, 6 and 9 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 1-4, 6 and 9 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

Claims 1-4, 6 and 9 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6 and 9 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Vik et al., (Int Arch Allergy Immunol, 1993, 101:89-94) as evidenced by Gajhede et al., as evidenced by Friedl-Hajek et al., (Molecular Immunology, 1999, 639-645) and as evidenced by Mandler et al. (J. Immunol. 1993, 150:407-418).

Claims 1 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vik et al., as evidenced by Gajhede et al., as evidenced by Friedl-Hajek et al., and as evidenced by Mandler et al., in view of Harlow et al. (Antibodies, A Laboratory Manual, 1988, Cold Spring Harbor Laboratory, pages 72-87).

The claim amendments are in order to more particularly define and distinctly claim applicants' invention and/or to better recite or describe the features of the present invention as claimed. No new matter is believed to be added.

Rejections under 35 U.S.C. § 102(b)

Claims 1-3, 7, and 9 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ferreira et al., (FASEB J, 1998, 12:231-242) as evidenced by Gajhede et al. (Ref. AD1 of 6/20/2002 IDS). According to the Examiner, Ferreira et al. teach pharmaceutical compositions comprising birch pollen allergen Bet v1 variants, said variants including 6 polypeptides having a single point mutation from a Bet v1 sequence, as well as a polypeptide that comprises all six of the individual mutations. The Examiner further alleges that the sequence of the polypeptides disclosed by Ferreira et al. comprise at least five consecutive solvent exposed amino acids as evidenced by the solvent accessibility data presented in Figure 2A of Gajhede et al. and that the solvent exposed amino acids appear on the surface of the protein within an approximately 500 square angstrom patch based upon the NMS and crystallographic structure data presented by Gajhede et al. Applicants disagree and now traverse as follows.

Applicants vigorously disagree with the Examiner that a peptide which “has a length of 8 to 50 amino acids” can be broadly and reasonably interpreted to mean a peptide comprising at least 8 amino acids without a upper limit on the number of amino acids. Applicants respectively believe that it is a misapplication of whatever guidelines the Examiner is working with since “8 to 50” explicitly denotes a range and it is implausible to assert that a structure which “has a range” may be reasonably considered to have a lower limit and not an upper limit. Applicants are very much afraid that the Examiner may be reconstructing the teachings of Ferreira et al. in order to find a basis for disallowing the present invention and respectfully remind the Examiner that hindsight gained by reviewing the current application may not be used to fashion rejections thereto.

For instance, no where do Ferreira et al. teach the use of fragments of Bet v1 allergens as potential immunotherapeutic agents. In fact, Ferreira et al. could not be more explicit when it declared that “**All** isoallergen mutants presented here and their corresponding amino acid substitutions are schematically shown in Figure 1.” Page 234, column 2, last three lines of paragraph 1. The entire teachings of Ferreira et al. is captured in their Abstract where it was declared: “We found that IgE binding to Bet v1 depended on **at least six amino acid** residues/positions. Immunoglobulin analyses and

inhibition experiments showed that the **multiple-point** Bet v1 mutant exhibited extremely low reactivity with serum IgE from birch pollen-allergic patients.” Page 231. On page 232, column 1, paragraph 3, Ferreira et al. declared: “By using a method developed to predict functional residues in proteins, we obtained a list of most common residues likely to influence IgE binding to Bet v 1... Based on the results of this analysis, we introduced point mutations at critical positions in the sequence of Bet v 1 ..” On page 232, column 2, paragraph 3, Ferreira et al. teaches: “To generate a Bet v1a construct carrying six-point mutations, the following approach was used.”

Thus Ferreira et al. was concerned about the effect of point mutations on amino acids at positions 10, 30, 57, 112, 113 and 125 of the **entire** Bet v 1a and Bet v1d molecules and how that affects their respective IgE binding capacity. No where therefore, did Ferreira explicitly or implied teach the use of peptides, obtained from Bet v1, 8 – 50 amino acids long, having at least three amino acids identical to at least three solvent-exposed amino acids of an allergenic protein which appear in close vicinity on the molecular surface of the allergenic protein.

The Examiner asserts that while Ferreira does not teach the use of fragments of their Bet v 1 single point or six-point mutants, but that they do teach the use of Bet v1 peptides. As the Examiner is aware, anticipation must be found in a single reference; other references may be used only to interpret the allegedly anticipating reference. *Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.* 726 F.2d 724, 220 USPQ 841 (Fed. Cir. 1984). But, referring to Ebner et al., the Examiner contends that “peptides per se are taught.” By so doing, the Examiner is not using Ebner et al. for interpretive purposes, but using Ebner et al. to fill in the deficiencies in Ferreira in order to form a basis for this rejection

Applicants contend that mere teaching of peptides, without more in reference to any particular protein, is not legally sufficient to preclude the patentability of those peptides. Assuming for the sake of argument that Ferreira teaches “peptides” of Bet v 1 a, the Examiner has not even averred, let alone shown that those “peptides” are being taught for the same use as those of the present invention; new and unobvious uses of known compounds being sufficient, as it were, for patentability. As the Examiner is aware, anticipation requires that every element of the claimed invention must be

identically shown in a single reference and those elements must be arranged as in the claim under review. In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Not only does Ferreira not teach peptides, it does not teach ones 8 to 50 amino acids long, having the unique structural characteristics of at least three amino acids in common with solvent-exposed amino acids of the wild type allergen; said peptide being used. For at least the foregoing, Applicants believe that there is no basis for maintaining this ground for rejection and respectfully request that it be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-4, 6 and 9 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Also, claims 1-4, 6 and 9 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

The Examiner asserts that Applicants have claimed a broad genus of composition comprising peptides wherein each of the peptide is identical to birch pollen allergen Bet v 1 all positions except one but the specification did not disclose a full length Bet v 1 polypeptide sequence.

This ground for rejection is now moot in view of amendments expressly limiting the immunotherapeutic agents of the present invention to peptides, 8 to 50 amino acids in length, having amino acid sequences identical to at least three solvent-exposed amino acids of Bet v1 protein and capable of inducing IgG antibody production without eliciting IgE mediated allergic reactions. The structural limitation being claimed is therefore with respect to a relatively short fragment of the Bet v 1 protein, namely between 8 and 50 amino acids in length, modified to differ in critical respects with the native sequence to at the very least have three solvent-exposed amino acids in common and more broadly to differ by one amino acid or less provided said peptide induces IgG production and does not induce a significant IgE response.

The Examiner further asserts that the structure of the peptide required to provide the functional properties of not being bound by IgE from birch pollen allergic patients but that does elicit an IgG response that binds the full length Bet v1 allergen is not readily apparent because the specification does not disclose the structure or amino acid sequence

required to give rise to these functional properties. Applicants respectfully disagree.

The ability to elicit IgG or IgE production or for that matter, elicit IgG production without eliciting IgE production have structure defining properties that are readily apparent to one of skill in the art. Allergens by definition contain T-cell epitopic sites. Thus the polypeptides described by Ferreira and Gaijhede contain most of the Bet v 1 specific T-cell epitopes whereas the peptides of the present invention, by inducing little or no significant IgE reaction, lack all of the Bet v 1 specific T-cell epitopes. Similarly, the Ebner et al. peptides differ fundamentally from those of the present invention. The Ebner peptides are peptides recognized by T-cells via their T-cell receptor. They result from proteolytic cleavage of the allergen and subsequent presentation to the T-cells via MHC class II. Further, the Ebner peptides cannot induce IgG antibody response nor do they react with IgG antibodies.

In that regard, the recitation of functional limitations which further define the structure of the peptides claimed patentably differentiates the peptides of the present invention from the prior art as cited and further obviates the Examiner's rejections on the basis of lack of enablement and insufficiency of the written description. Peptides of the present invention can be made by synthetic means or by proteolytic digestion of Bet v 1. Armed with the teaching in the specification that surface exposed Bet v1-derived peptides lack IgE binding capacity and allergenic activity, that the peptide must be 8 to 50 amino acids in length, and that the peptide must have at least three preferably consecutive amino acids corresponding to surface exposed amino acids, one of skill in the art can readily determine the immunotherapeutic agents of the present invention by administering said peptides to a an immunological test animal and assaying its sera for the degree of IgG production. The method of making the peptides of the present invention is therefore sufficiently enabled and Applicants had full possession of the invention as claimed as at the filing date of the Application.

For at least these reasons, Applicants respectfully ask that the Examiner reconsider and withdraw all rejections based on 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-4, 6 and 9 are rejected under 35 U.S.C. §112, second paragraph, as

allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that the metes and bounds of the claimed subject matter is unclear because the Application failed to recite a Bet v 1 reference sequence in spite of their being a large number of Bet v 1 sequences known in the art. Applicants respectfully disagree and traverse as follows.

Applicants appreciate that there are different mutants of Bet v 1 allergens, however the claims as amended are not unclear because they are not referenced to a particular Bet v 1 mutant. Where as here, Applicants are claiming a relatively short segment of Bet v 1, having at least three amino acids identical to surface exposed amino acids, and further teaching that the segment lacks T cell epitopic sites, and further teaching that the segment does not have any secondary structure, and further teaching, how using an immunological model, the sequences of interest can be identified, it is respectfully submitted that there is no basis for an indefiniteness rejection. By asserting this rejection, the Examiner is in effect stating that Applicants are not entitled to any Bet v 1-derived immunotherapeutic agents except ones whose primary structures are explicitly disclosed. Applicants believe that given an allergen of known three dimensional structure, one of skill in the art can easily attain the sequences of the present invention by selecting short sequences thereof encompassing surface exposed amino acids, having readily verifiable IgG focusing properties, and those sequences, however many they are, fall squarely within the ambit of the present invention. As such, there is no basis for maintaining this ground for rejection and Applicants respectfully ask that it be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 1-4, 6 and 9 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Vik et al., (Int Arch Allergy Immunol, 1993, 101:89-94) as evidenced by Gajhede et al., as evidenced by Friedl-Hajek et al., (Molecular Immunology, 1999, 639-645) and as evidenced by Mandler et al. (J. Immunol. 1993, 150:407-418). The Examiner asserts that Vik et al teaching peptides derived from Bet v 1 but does not teach that their peptide upon administration produce a protective IgG response.

Applicants contend that Vik et al. can neither anticipate the claimed invention nor

render it obvious. The peptides as taught by Vik et al. encompass a single haptenic epitope (see Abstract). That means that such peptides can react with the IgE antibodies of patients. Indeed on page 91, right column, last but one paragraph, Vik et al. declared: "An inhibition of more than 20% was obtained at peptide concentrations of 277 nM or higher, confirming a specific IgE binding under the experimental conditions." As amended, the peptides of the present invention differ patentably from those of Vik et al. by not inducing IgE-mediated reactions.

Directing the Examiner's attention to page 92, left-hand column, last paragraph under the heading "Nasal provocation test," Vik et al. explicitly declared that BSA conjugated Bet v1 23-38 caused sneezing and itching after 15-60 seconds. This clearly demonstrates that the Vik peptide not only reacts with IgE antibodies, but also causes allergic reactions in the nose of patients. Without listing the primary sequences of all the different peptides that are encompassed by this invention, it is clear that induction of IgG antibody production and **lack of T-cell epitopic sites**, structurally distinguishes the peptides of the present invention from those of Vik et al. For at least that reason, Applicants respectfully ask the Examiner to reconsider and withdraw this ground for rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vik et al., as evidenced by Gajhede et al., as evidenced by Friedl-Hajek et al., and as evidenced by Mandler et al., in view of Harlow et al. (Antibodies, A Laboratory Manual, 1988, Cold Spring Harbor Laboratory, pages 72-87).

The Examiner asserts that Vik et al. teach multiple peptides from the amino terminal region of the Bet v1 allergen and detail the coupling of the Bet v I 23-28 peptide to BSA for use in pharmaceutical compositions. The Examiner admits that Vik's peptides do not differ from Bet v 1 sequences by one amino acid difference. The Examiner further asserts that Harlow et al. teach that peptide conjugation should be performed so that the coupled peptide is linked by its carboxyl- or amino terminal residue to the larger protein, and that sulphydral coupling cyteines are useful for such purposes. The Examiner

concludes that it would have been obvious to combine Vik et al. and Harlow et al. in order to arrive at the present invention.

Applicants hereby reassert their foregoing contentions as if they have been incorporated herein by reference. Without admitting that there is sufficient motivation in the cited arts to make the combination which the Examiner deems obvious, Applicants vigorously contend that the combination of Vik et al. and Harlow et al. will not arrive at the present invention. As amended, the peptides of the present invention will not provoke IgE allergic reactions and are thus structurally and functionally different from any peptide which Vik et al. teach. And that deficiency is not cured by Harlow et al. which allegedly teaches the coupling of terminal amino acids to BSA. For that at least, Applicants assert that there is no basis for the obviousness type rejection and respectfully request that it be withdrawn.

CONCLUSION

All of the stated grounds for rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn and the claims allowed to issue. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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